

WE CLAIM:

- [C1]** A method for modulating pathways leading to programmed cell death, said method comprising:
- (a) selecting a target within the JNK pathway; and
 - (b) interfering with said target by an agent that either upregulates or downregulates the JNK pathway.
- [C2]** The method of claim 1, said method comprising:
- (a) obtaining an agent that is sufficient to block the suppression of JNK activation by Gadd45 proteins; and
 - (b) contacting the cell with said agent to increase the percent of cells that undergo programmed cell death.
- [C3]** The method of claim 2, wherein the agent is an antisense molecule to a *gadd45 β* gene sequence or fragments thereof.
- [C4]** The method of claim 2, wherein the agent is a small interfering RNA molecule (siRNA).
- [C5]** The method of claim 2, wherein the agent is a ribozyme molecule.
- [C6]** The method of claim 2, wherein the agent is a cell-permeable peptide fused to JNKK2 that effectively competes with the binding site of Gadd45 β .
- [C7]** The method of claim 2, wherein the agent is a small molecule.
- [C8]** The method of claim 6, wherein the molecule is a peptide mimetic that mimics the functions of a Gadd45 protein.
- [C9]** The method of claim 1, said method comprising:
- (a) interfering with the target by obtaining a molecule that suppresses JNK signaling by interacting with a Gadd45-binding region on JNKK2; and
 - (b) contacting a cell with the molecule to protect the cell from programmed cell death.
- [C10]** The method of claim 9, comprising:
- (a) obtaining a cDNA molecule that encodes a full length or portions of a Gadd45 protein;
 - (b) transfecting the cell with the cDNA molecule; and

- (c) providing conditions for expression of the cDNA in the cell so that JNKK2 is bound and unavailable to activate the JNK pathway that induces programmed cell death.

- [C11]** The method of claim 10, wherein the cDNA molecule encodes a fragment of Gadd45 protein that is sufficient to suppress JNK signaling.
- [C12]** The method of claim 10, wherein the cDNA molecule encodes a peptide that corresponds to amino acids 69-113 of Gadd45 β .
- [C13]** The method of claim 10, wherein the programmed cell death is induced by TNF α .
- [C14]** The method of claim 10, wherein the programmed cell death is induced by Fas.
- [C15]** The method of claim 10, wherein the programmed cell death is induced by TRAIL.
- [C16]** The method of claim 10, wherein the programmed cell death is induced by a genotoxic agent.
- [C17]** The method of claim 16, wherein the agent is selected from the group consisting of daunorubicin and cisplatin.
- [C18]** A method to identify agents that modulate JNK signaling, said method comprising:
 - (a) determining whether the agent binds to Gadd45 β ; and
 - (b) assaying for activity of the bound Gadd45 β to determine the effect on JNK signaling.
- [C19]** A method for obtaining a mimetic that is sufficient to suppress JNK activation by interacting with JNKK2, said method comprising:
 - (a) designing the mimetic to mimic the function of a Gadd45 protein;
 - (b) contacting the mimetic to a system that comprises the JNK pathway; and
 - (c) determining whether there is suppression of JNK signaling.
- [C20]** A method for screening and identifying an agent that modulates JNK pathway *in vitro*, said method comprising:
 - (a) obtaining a target component of the JNK pathway;
 - (b) exposing a cell to the agent; and
 - (c) determining the ability of the agent to modulate the JNK pathway.

[C21] The agent in claim 20, is selected from a group consisting of peptides, peptide mimetics, peptide-like molecules, mutant proteins, cDNAs, antisense oligonucleotides or constructs, lipids, carbohydrates, and synthetic or natural chemical compounds.

[C22] A method for screening and identifying an agent that modulates JNK activity *in vivo*, said method comprising:

- (a) obtaining a candidate agent;
- (b) administering the agent to a non-human animal; and
- (c) determining the level of JNK activity in the animal compared to JNK activity in animals not receiving the agent.

[C23] A method for identifying an agent that prevents Gadd45 β from blocking apoptosis, said method comprising:

- (a) contacting cells that express high levels of Gadd45 β which are protected against TNF α -induced apoptosis with the agent and TNF α ;
- (b) comparing apoptosis in the cells in (a) with control cells exposed to the agent but not to TNF α ; and
- (c) inferring from differences in apoptosis in treated versus control cells, whether the agent prevents Gadd45 β from blocking apoptosis.

[C24] A method for screening for a modulator of the JNK pathway, said method comprising:

- (a) obtaining a candidate modulator of the JNK pathway, wherein the candidate is potentially any agent capable of modulating a component of the JNK pathway, including peptides, mutant proteins, cDNAs, anti-sense oligonucleotides or constructs, synthetic or natural chemical compounds;
- (b) administering the candidate agent to a cancer cell;
- (c) determining the ability of the candidate substance to modulate the JNK pathway, including either upregulation or downregulation of the JNK pathway and assaying the levels of up or down regulation.

[C25] A method of treating degenerative disorders and other conditions caused by effects of apoptosis in affected cells, said method comprising:

- (a) obtaining a molecule that interferes with the activation of JNK pathways; and
- (b) contacting the affected cells with the molecule.

[C26] A method of aiding the immune system to kill cancer cells by augmenting JNK signaling, said method comprising:

- (a) obtaining an inhibitor to block JNK signaling; and
- (b) contacting the cancer cells with the inhibitor.

[C27] The method of claim 26, wherein the inhibitor blocks activation of JNKK2 by Gadd45 β .

[C28] A method for transactivating a *gadd45 β* promoter, said method comprising:

- (a) binding NF- κ B complexes to promoter elements of *gadd45 β* ; and
- (b) assaying for *gadd45 β* gene expression.

[C29] A method for treating cancer, said method comprising:

- (a) increasing JNK activity by inhibiting Gadd45 β function; and
- (b) administering inhibitors that interfere with Gadd45 β function.

[C30] A method to determine agents that interfere with binding between Gadd45 protein and JNKK2, said method comprising:

- (a) obtaining an agent that binds to Gadd45 protein;
- (b) contacting a cell with the agent under conditions that would induce transient JNK activation; and
- (c) comparing cells contacted with the agent to cells not contacted with the agent to determine if the JNK pathway is activated.

[C31] A molecule with a nucleotide sequence having Gene Bank Acc. # AF441860 that functions as a *gadd45 β* promoter.

[C32] A molecule with a nucleotide sequence that is an element of the promoter at amino acid positions selected from the group consisting of positions -447/-438 ($\kappa\beta$ -1), -426/-417 ($\kappa\beta$ -2), -377/-368 ($\kappa\beta$ -3) according to FIG. 8.

[C33] A molecule comprising a region of Gadd45 β , characterized by the amino acid sequence from positions 60-114 of the full length of Gadd45 β protein.

[C34] A molecule comprising a binding region of JNKK2 characterized by the amino acid sequence from positions 132-156 (GPVWKMRFRTGHVIAVKQMRRSGN) of the full length JNKK2.

[C35] A molecule comprising a binding region of JNKK2 characterized by the

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amino acid sequence from positions 220-234 (GKMTVAIVKALYYLK) of the full length JNKK2.